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AHRQ's Comparative Effectiveness Research on Oral Medications for Type 2 Diabetes: A Summary of the Key Findings

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AHRQ's Comparative Effectiveness Research on Oral Medications for Type 2 Diabetes: A Summary of the Key Findings

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Target Audiences

This CME activity is designed to meet the educational needs of physicians, pharmacists, nurses, and case managers.

Learning Objectives

Based on the findings from AHRQ's comparative effectiveness review of reseach on oral medications, noninsulin injectable medications, and insulins for type 2 diabetes:

1. Describe the comparative benefits of treatment options on intermediate measures of glycemic control and on long-term morbidity and mortality outcomes.
2. Compare the harms of treatment options based on risks of adverse events including hypoglycemia, liver injury, congestive heart failure, and pancreatitis.
3. Summarize the gaps in current knowledge regarding the comparative benefits and harms of treatment options across prespecified patient subpopulations.

Funding

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AHRQ's Comparative Effectiveness Research on Oral Medications for Type 2 Diabetes: A Summary of the Key Findings

Wendy L. Bennett, MD, MPH; Lisa M. Balfe, MPH; and Joanne M. Faysal, MS

ABSTRACT

BACKGROUND: In 2007, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review on the comparative effectiveness of oral medications for type 2 diabetes. The review included studies on the benefits and risks of oral medications used for achieving glycemic control in patients with type 2 diabetes. AHRQ published an updated review in March 2011 that summarized the benefits and harms of medications (metformin, second-generation sulfonylureas, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists), as monotherapy and in combination, for the treatment of adults with type 2 diabetes.

OBJECTIVES: To (a) familiarize health care professionals with the methods and findings from AHRQ's 2011 comparative effectiveness review on medications for adults with type 2 diabetes, (b) encourage consideration of the clinical and managed care applications of the review findings, and (c) identify limitations and gaps in the existing research with respect to the benefits and risks of diabetes medications.

SUMMARY: Type 2 diabetes mellitus is a major public health burden. Since the 2007 AHRQ systematic review of oral medications for type 2 diabetes, the FDA has approved several new drug classes. Therefore, in 2011, the original systematic review was updated with comparisons including the newer oral diabetes medications. The updated report expands beyond the scope of the original 2007 review by including comparisons of 2-drug combinations and the addition of more head-to-head comparisons, as well as additional adverse outcomes. A high strength of evidence showed that most medications were similarly efficacious at lowering hemoglobin A1c by about 1 absolute percentage point compared with baseline values. The addition of most oral medications to initial monotherapy further improved glycemic control by lowering A1c by another 1 percentage point. The only exception was the DPP-4 inhibitor class, which did not lower A1c to the same extent as metformin when used as monotherapy. Overall, metformin was found to have a more favorable effect on body weight when compared with other medications. Two-drug combinations compared with each other demonstrated similar reductions in A1c levels. Metformin decreased low-density lipoprotein cholesterol (LDL-C) relative to pioglitazone, sulfonylureas, and DPP-4 inhibitors. Sulfonylureas had a 4-fold higher risk of mild-to-moderate hypoglycemia compared with metformin alone, and, in combination with metformin, had more than a 5-fold increased risk compared with metformin plus a thiazolidinedione. Thiazolidinediones had an increased risk of congestive heart failure relative to sulfonylureas, and an increased risk for bone fractures relative to metformin. Diarrhea occurred more often for metformin users compared with thiazolidinedione users. Although the long-term risks and benefits of diabetes medications remain unclear, the evidence supports the use of metformin as a first-line agent.

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In recent years, clinicians have witnessed major advances in the development of oral medications for controlling hyperglycemia associated with type 2 diabetes mellitus. In 1995, sulfonylureas and insulin were the only available drug classes for patients affected by the disease.[1] As of early 2012, 11 classes of medications are FDA-approved for treating type 2 diabetes, including biguanides (e.g., metformin), thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, glucagon-like peptide-1 (GLP-1) receptor agonists, an amylin analogue, bromocriptine, alpha-glucosidase inhibitors, the bile acid sequestrant colesevelam, and insulins. With the increased number of options, clinicians and their patients face difficult decisions regarding appropriate treatment regimens. The situation is compounded by the fact that many patients need 2 or more medications to achieve recommended glycemic control over time. From 2000 to 2006, the proportion of U.S. adults who took 3 or more classes of diabetes medications increased from 6% to 14%. Additionally, 35% of patients with diabetes took medications from 2 classes.[2] With the introduction of many new antidiabetic agents into the market, an evaluation of their effectiveness and safety is needed.

In 2007, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of oral medications for adults with type 2 diabetes.[3] The review included 216 studies that evaluated intermediate and clinical outcomes in patients taking medications approved at that time. Key results indicated that most antidiabetes agents reduced hemoglobin A1c by a similar magnitude. Compared with metformin, most oral medications in monotherapy and combination were associated with an increased average weight gain of 2 kg, and only metformin decreased LDL-C. Moreover, metformin was associated with increased risks of gastrointestinal (GI) problems, while sulfonylureas and thiazolidinediones were associated with hypoglycemia and heart failure, respectively.[3] Few studies included in the 2007 review assessed the comparative effects of the drugs on microvascular and macrovascular complications.

Since the 2007 AHRQ review, the U.S. Food and Drug Administration (FDA) approved 2 new classes of drugs: injectable incretin (GLP-1 receptor agonist) mimetics and oral DPP-4 inhibitors. Exenatide and liraglutide, the injectable incretin mimetics, were approved in 2005 and 2010, respectively. Sitagliptin and saxagliptin, both DPP-4 inhibitors, were approved in 2006 and 2009, respectively. The approval of these medications, along with the publication of new studies with head-to-head comparisons of oral diabetes medications motivated AHRQ's commission of an updated comprehensive review of published studies. In March 2011, the John Hopkins University Evidence-Based Practice Center (EPC) published the updated comparative effectiveness

TABLE 1 Comparisons of Oral Diabetes Monotherapies and Combination Therapies

	Main Intervention	Comparisons
Monotherapy as main intervention	Metformin	Thiazolidinedione; Sulfonylurea; DPP-4 inhibitor; Meglitinides; GLP-1 agonist; Combination of metformin plus thiazolidinedione; Combination of metformin plus sulfonylurea; Combination of metformin plus DPP-4 inhibitor; Combination of metformin plus meglitinides
	Thiazolidinedione	Different thiazolidinedione; Sulfonylurea; DPP-4 inhibitor; Meglitinides; GLP-1 agonist
	Sulfonylurea	DPP-4 inhibitor; Meglitinides; GLP-1 agonist
	DPP-4 inhibitor	DPP-4 inhibitor; Meglitinides; GLP-1 agonist
	Meglitinide	GLP-1 agonist
Combination therapy as main intervention	Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinide or DPP-4 inhibitor or GLP-1 agonist)	Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist)
	Combination of metformin plus (a thiazolidinedione or a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist)	Combination of a thiazolidinedione plus (a sulfonylurea or a meglitinides or DPP-4 inhibitor or GLP-1 agonist)

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.

review.[1] The 2011 review integrated evidence from the previous report with current research, including direct comparisons of oral medication as monotherapy and in 2-drug combinations, as well as medications combined with basal or premixed insulin.

Systematic Review Methods

This section summarizes the methods by which the updated comparative effectiveness review was conducted. Complete details about the methods are provided in the full technical report.[1]

Key Questions and Comparisons

The EPC investigators were guided by 4 key clinical questions, which pertained to adults aged 18 years or older with a diagnosis of type 2 diabetes mellitus. The questions are paraphrased as follows:

1. Intermediate outcomes: What are the comparative effects of various treatment options on the intermediate outcomes of glycemic control as measured by A1c, body weight, and lipids, including LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides?
2. Long term outcomes: What are the comparative effects of various treatment options on long-term clinical outcomes, including all-cause mortality, cardiovascular mortality, cardiovascular and cerebrovascular morbidity (e.g., myocardial infarction and stroke), retinopathy, nephropathy, and neuropathy?
3. Adverse effects: How do the various treatment options compare with regard to risks of adverse events and side effects?
4. Differences in subgroups: Do the safety and effectiveness of treatment options differ across patient subgroups, especially for adults aged 65 or older?

For each key question, the investigators sought studies that included the priority medication comparisons indicated in Table 1.

Literature Search and Study Selection

Studies included in the AHRQ review were identified through comprehensive searches of biomedical literature using MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. The database searches comprised periods from database inception through April 2010. In addition, the literature search included medical reviews with safety information, scientific discussion sections of the European Public Assessment Reports, Health Canada Product Monographs, and public registries of clinical trials. Whereas the updated review included additional medications and long-term clinical outcomes, the search strategy was similar to that conducted for the 2007 review.[3]

The 2011 review included medications that were not evaluated in the original review: DPP-4 inhibitors; GLP-1 receptor agonists; combinations of metformin plus a DPP-4 inhibitor, a meglitinide, basal insulins including neutral protamine Hagedorn (NPH), detemir, and glargine, or a premixed insulin; and the combination of a thiazolidinedione plus a meglitinide. In addition, extending beyond the 2007 review, the updated review evaluated the comparative effects of treatment options on outcomes of fractures, cholecystitis, and macular edema.

All of the studies included in the 2011 review enrolled patients with type 2 diabetes. The investigators excluded studies on patients with type 1 diabetes, impaired glucose tolerance, metabolic syndrome, maturity-onset diabetes of youth, and gestational diabetes. To be included in the review, studies had to be reported in English-language articles, last more than 3 months, and have more than 40 total subjects. Studies that did not apply to the predefined outcomes listed in the key questions were also excluded. To answer key question 1, the investigators selected only randomized controlled trials (RCTs). Studies that addressed key questions 2 and 3 included RCTs, nonrandomized trials, cohort studies with comparison groups, and case-control studies. Crossover studies were included for evaluations of hypoglycemia, liver injury, and GI side effects.

Evaluations of Study Quality and Rating the Strength of the Body of Evidence

EPC investigators independently assessed the quality of each included study based on the Jadad criteria, which included appropriateness of randomization scheme, blinding, and description of withdrawals and dropouts.[4] Investigators assessed quality of observational studies using items about the study setting, inclusion and exclusion criteria, key characteristics of subjects, treatment details, outcome details, statistical analyses, and losses to follow-up.

Overall study quality for all studies was assessed as good, fair, or poor based on the risk for bias. Studies rated as good had the least bias, with formal randomized designs and results that were considered valid and devoid of reporting errors. Fair studies were susceptible to some bias and had missing information, while poor studies had high risk of bias with errors in reporting, and design flaws that might have invalidated the results.

At the completion of the review, the EPC investigators graded the strength evidence for each outcome by comparison of interest using criteria recommended by the AHRQ Guide for Conducting Comparative Effectiveness Reviews.[5] Investigators assessed the strength of evidence by the evaluating the number of included studies, strength and quality of study design, consistency of results, directness of the outcome measurements with clinically relevant outcomes, precision, and the magnitude of the effect. The evidence was graded as high, moderate, low, or insufficient. For example, high strength of evidence indicated high confidence that the evidence available reflects the true effect, and further research would be unlikely to change the estimate. A grade of insufficient indicates that the evidence is not available.

Monotherapy Comparisons

Table 1 shows the priority head-to-head monotherapy comparisons of metformin, thiazolidinediones, second-generation sulfonylureas, DPP-4 inhibitors, meglitinides, and GLP-1 agonists. For outcomes of A1c, weight, and LDL-C, we summarized the monotherapy comparisons in Figures 1-4, which presented the pooled between-group differences and strength of evidence.

Comparative Effects of Monotherapy Interventions on A1c

Most monotherapy comparisons had similar absolute reductions in A1c by approximately 1% compared with baseline values, with nonsignificant pooled between-group differences (Figure 1). Meta-analyses of 14 RCTs that compared metformin with a thiazolidinedione[6-19] and 17 RCTs[12,13,15,20,21-33] comparing metformin with a sulfonylurea showed no significant differences between the treatment arms. Studies comparing metformin with a sulfonylurea had substantial heterogeneity, which may be explained by study duration. Studies lasting less than 6 months seemed to slightly favor sulfonylureas, while those lasting 6 months to a year showed no differences between the groups.

Two long-term RCTs of patients newly diagnosed with type 2 diabetes, ADOPT and UKPDS, were excluded from the meta-analysis comparing metformin with sulfonylureas. The ADOPT (A Diabetes Outcome Progression Trial) trial and UKPDS (United Kingdom Prospective Diabetes Study) had conflicting results related to glycemic control. In the ADOPT trial, A1c was lowered to a greater extent in patients treated with metformin versus sulfonylurea after a median follow-up of 4 years.[34] In 1 UKPDS study that met inclusion criteria for this review (others were excluded because participants took multiple mediations making it impossible to discern combinations), sulfonylureas were favored over metformin in overweight individuals on monotherapy after 9 years of follow-up.[35] The EPC investigators speculated that the differences between these 2 large trials may be due to differences in types of sulfonylureas across studies, study duration, or study design.

Metformin was compared with meglitinides in 3 RCTs published in 4 articles.[36-39] The studies, which lasted 3 months to 1 year, showed similar effects on A1c reduction for both treatments.

In contrast to the findings from the short-term studies summarized thus far, a meta-analysis of 3 short-duration RCTs (reported in 4 publications) indicated with moderate strength of evidence that A1c was reduced by a greater magnitude in patients treated with metformin versus a DPP-4 inhibitor (pooled mean difference = –0.37%, 95% confidence interval [CI] = –0.54% to –0.20%).[40-43] In 1 RCT reported in 2 articles, the pooled between-group difference for A1c was –0.5%, favoring metformin over sitagliptin at both 24 and 54 weeks of follow-up.[40-41]

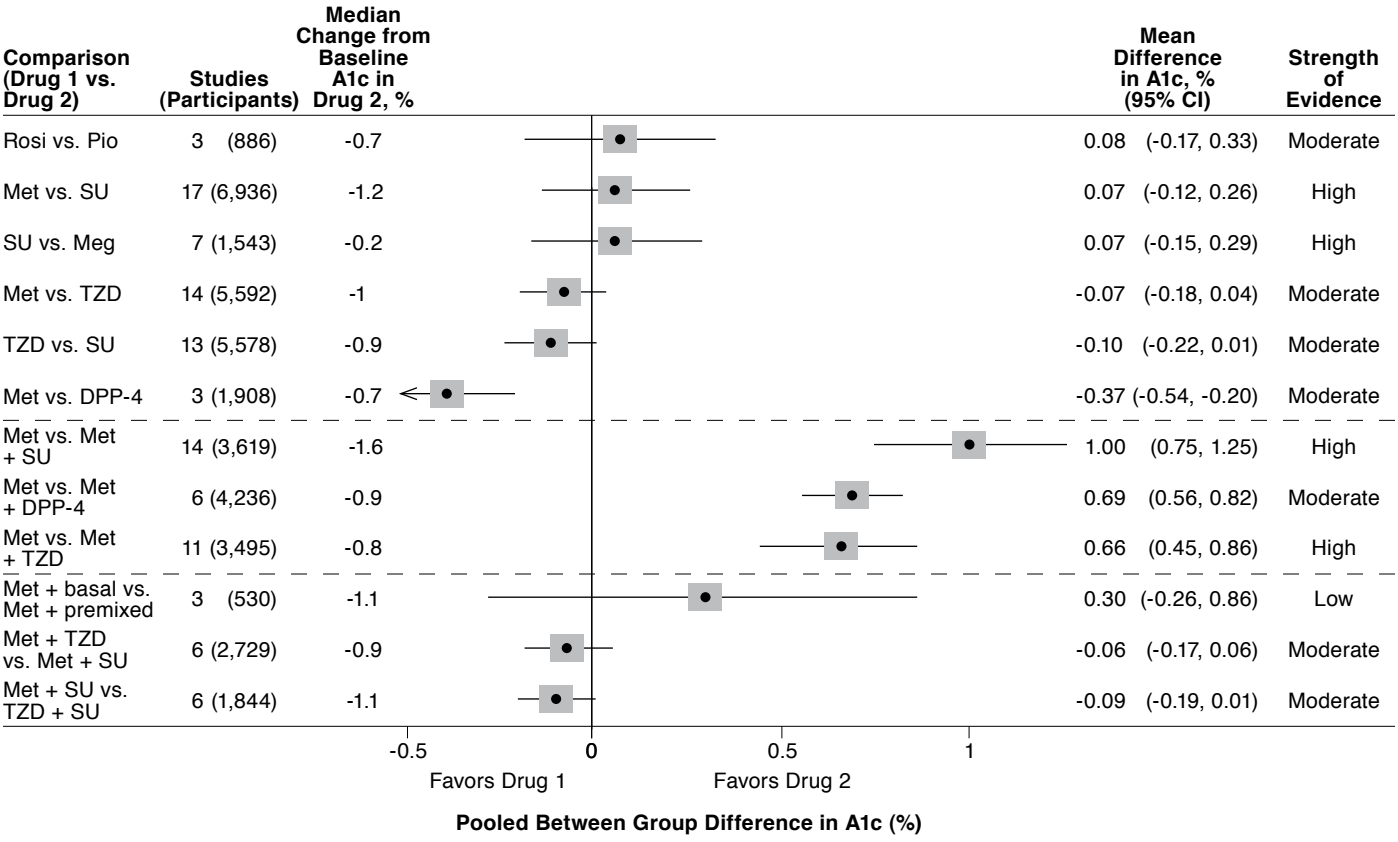
Pooled analyses indicated no differences in A1c reduction for comparisons between rosiglitazone and pioglitazone, sulfonylureas and meglitinides, and thiazolidinediones and sulfonylureas.

Comparative Effects of Monotherapies on Body Weight

For the outcome of changes in body weight, metformin generally maintained weight or was not associated with weight gain compared to sulfonylureas and thiazolidinediones which increased body weight (Figure 2). A meta-analysis of 8 RCTs at 1 year of follow-up or less found small body weight reductions in all metformin arms compared with generally small increases in body weight with thiazolidinediones (pooled between-group difference of –2.6 kg [95% CI = –4.1 kg to –1.2 kg] favoring metformin).[9-11,13,14,16,17,44] Metformin maintained or decreased weight when compared with sulfonylureas (pooled between-group difference of –2.7 kg [95% CI = –3.5 kg to –1.9 kg] favoring metformin)[13,23-33] and with DPP-4 inhibitors (pooled between-group difference of –1.4 kg [95% CI = –1.8 kg to –1.0 kg] favoring metformin).[40-43] Therefore, metformin was favored for lowering weight compared with other medications, with a mean difference in weight change of 1.4 kg to 2.7 kg (Figure 2).

In other monotherapy comparisons, a meta-analysis of 3 RCTs indicated that the GLP-1 agonist, liraglutide, was associated with less weight gain than sulfonylureas, which had moderate strength

FIGURE 1 Pooled Between Group Difference for A1c by Monotherapy and Combination Therapy Comparisons[a]



[a]*Reproduced from Figure 1 (page 605) in Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011;154(9):602-13.[141] Error bars represent 95% confidence intervals.*

A1c = hemoglobin A1c; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; Meg = meglitinide; Met = metformin; Pio = pioglitazone; premixed = premixed insulin; Rosi = rosiglitazone; SU = sulfonylurea; TZD = thiazolidinediones.

of evidence.[45-47] In a meta-analysis of 5 short-duration studies lasting 5 years or less, patients treated with sulfonylureas had less weight gain than patients treated with thiazolidinediones, which was graded as low strength of evidence.[13,48-51] No significant differences in body weight changes were found in comparisons between sulfonylureas and meglitinides, with a high grade for strength of evidence.

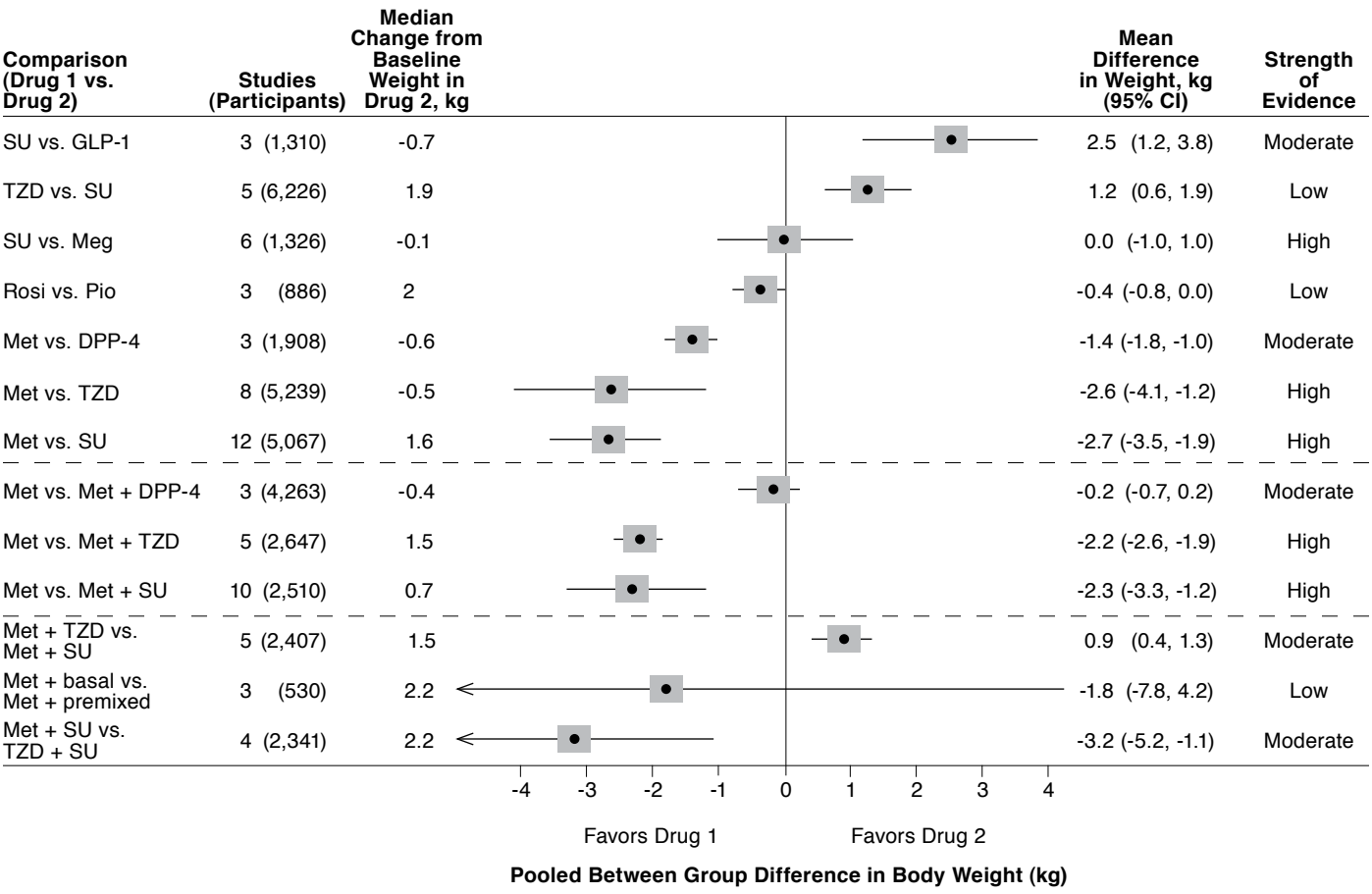
Comparative Effects of Monotherapies on Plasma Lipid Levels

The AHRQ review evaluated the comparative effects of oral diabetes monotherapies on LDL-C, HDL-C, and triglycerides. Metformin was generally associated with increased HDL-C and decreased LDL-C and triglycerides. In meta-analyses for LDL-C outcomes, studies comparing metformin with sulfonylureas,[22-24,26,29,30,32,52] pioglitazone,[6,9,14-16,19] rosiglitazone,[7,10,11,44,53,54] and DPP-4 inhibitors[41-43] resulted in greater reductions in LDL-C in the metformin arms. As presented in Figure 3, the mean differences in LDL-C reduction between metformin and DPP-4 inhibitors, sulfonylureas, rosiglitazone, and pioglitazone ranged from 5.9 mg per dL to 14.2 mg per dL. Additionally, rosiglitazone raised LDL-C levels significantly more than pioglitazone.[55-57]

Pioglitazone increased HDL-C more so than metformin,[6,9,12-16,19] rosiglitazone,[55-57] and sulfonylureas in pooled analyses.[12,13,50,58-60] For these comparisons, pooled between-group differences ranged from +0.5 mg per dL to +4.3 mg per dL. Changes in HDL-C were similar in comparisons of metformin with sulfonylureas or rosiglitazone.

In a meta-analysis of 8 RCTs, triglyceride levels were reduced significantly more in patients treated with pioglitazone than metformin (mean pooled difference = –27.2 mg per dL, 95%

FIGURE 2 Pooled Between Group Difference for Body Weight by Monotherapy and Combination Therapy Comparisons[a]



[a]*Reproduced from Figure 2 (page 606) in Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011;154(9):602-13.*[141] *Error bars represent 95% confidence intervals.*

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1; kg = kilogram; Meg = meglitinide; Met = metformin; Pio = pioglitazone; premixed = premixed insulin; Rosi = rosiglitazone; SU = sulfonylurea; TZD = thiazolidinediones.

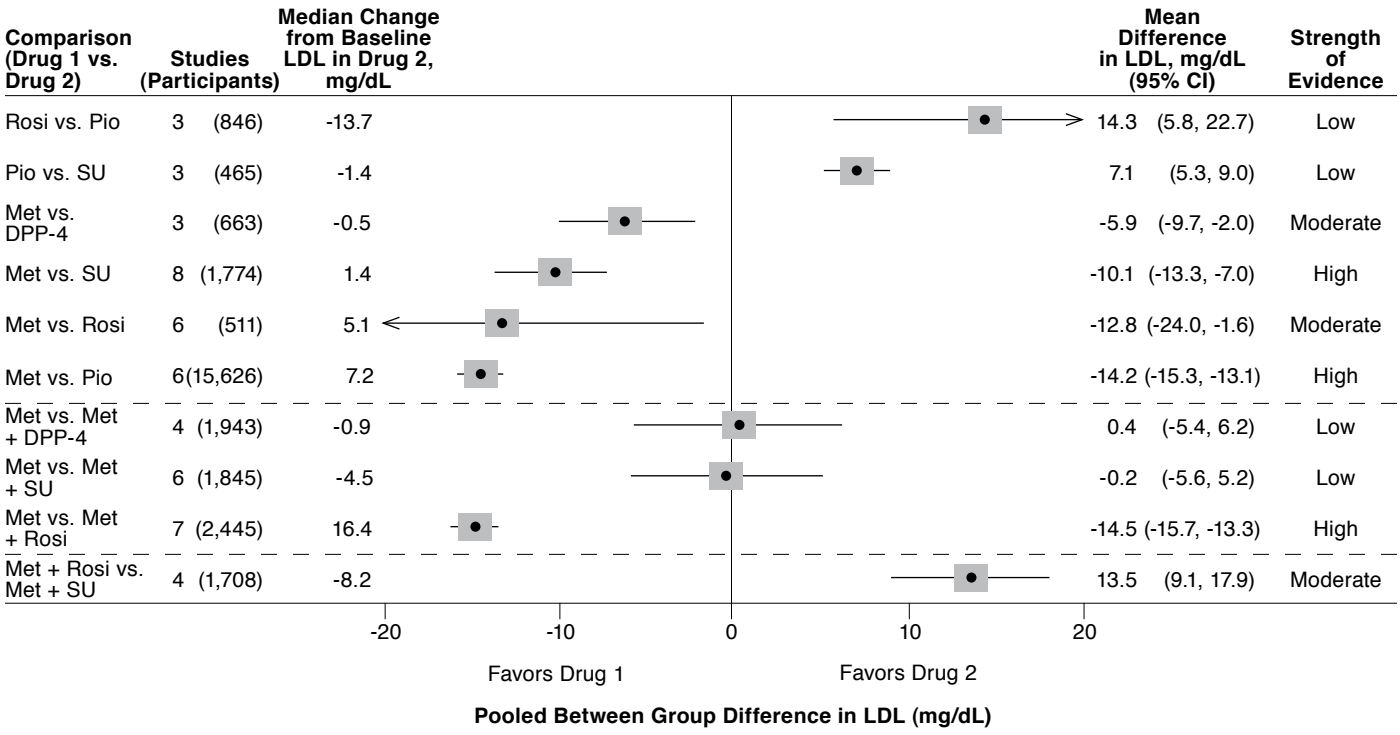
CI = –30.0 mg per dL to –24.4 mg per dL).[6,9,12-16,19] However, metformin decreased triglyceride levels more so than rosiglitazone (mean pooled difference = –26.9 mg per dL, 95% CI = –49.3 mg per dL to –4.5 mg per dL).[7,10,11,44,53,54] In addition, in a meta-analysis of 11 RCTs comparing metformin with sulfonylureas, metformin was associated with greater reductions in triglycerides (mean pooled difference = –8.6 mg per dL, 95% CI = –15.6 mg per dL to –1.6 mg per dL).[12,13,22-24,26,28-30,32,33] Similar effects on triglyceride levels were found in 4 RCTs comparing sulfonylureas with meglitinides.[60-63]

Comparative Effects of Monotherapies on Long-Term Clinical Outcomes

Although the updated AHRQ review included 41 studies that were published since the 2007 review, most of the new studies followed patients for less than 1 year and did not report long-term clinical events such as death and cardiovascular events. For several comparisons, including those with the DPP-4 inhibitors, GLP-1 agonists, and meglitinides, very few or no studies were available. The insufficient or low-strength evidence limited conclusions regarding the comparative effects of oral diabetes medications on long-term clinical outcomes. This section summarizes the key findings on long-term clinical outcomes from the updated review.

Regarding the comparative effects of metformin versus other oral medications on all-cause mortality, most comparisons had insufficient evidence or mixed findings. All-cause mortality was reported in the ADOPT study, a 4-year double-blind RCT that

FIGURE 3 Pooled Between Group Difference for LDL Cholesterol by Monotherapy and Combination Therapy Comparisons[a]



[a]*Reproduced from Figure 3 (page 607) in Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011;154(9):602-13.[141] Error bars represent 95% confidence intervals. To convert LDL values to mmol/L, multiply by 0.0259.*

CI = confidence interval; dL = deciliter; DPP-4 = dipeptidyl peptidase-4 inhibitor; LDL = low density lipoprotein; Met = metformin; mg = milligram; Pio = pioglitazone; Rosi = rosiglitazone; SU = sulfonylurea.

compared metformin (n = 1,454), rosiglitazone (n = 1,456), and the sulfonylurea glyburide (n = 1,441) as initial treatment for type 2 diabetes.[34] The total number of deaths was similar across treatment groups, ranging from 31-34 (2.1%-2.3%). In a cohort study of patients with type 2 diabetes included in the Saskatchewan Health registry, the adjusted odds ratio (OR) for all-cause mortality was significantly lower in those treated with metformin versus a sulfonylurea (OR = 0.60, 95% CI = 0.49 to 0.74).[64] Similar findings from comparisons of metformin and sulfonylureas were reported in several other cohort studies included in the AHRQ review.[1] However, the strength of evidence from this comparison was low because of inconsistent results between observational studies and RCTs and the lower quality of the study design of observational studies.

For cardiovascular mortality, the ADOPT trial reported 2, 2, and 3 fatal myocardial infarctions in the metformin, rosiglitazone, and sulfonylurea arms, respectively.[34] However, results of several cohort studies indicated that risks of cardiovascular mortality were slightly lower among patients treated with metformin versus sulfonylureas.[1] Based on data from the Saskatchewan Health registry,[65] metformin was associated with a lower cardiovascular mortality risk when compared with a sulfonylurea (adjusted hazard ratio [HR] = 0.76, 95% CI = 0.58-1.00). Consistent with these findings, a 5-year retrospective cohort study in Scotland (n = 5,730),[66] reported a higher cardiovascular mortality risk in patients treated with a sulfonylurea versus metformin (relative risk [RR] = 1.70, 95% CI = 1.18-2.45). In contrast, compared with glyburide, metformin was associated with a slightly higher risk for cardiovascular mortality in a prospective cohort study of Israeli patients with prior coronary artery disease.[67] Due to short study durations and low numbers of cardiovascular deaths in RCTs, the strength of evidence for these comparisons was rated low or insufficient.

For cardiovascular and cerebrovascular morbidity outcomes, most RCTs were of short duration and reported few events, making the strength of evidence low and limiting the precision of the results. Results from the ADOPT trial indicated minimal differences between metformin, rosiglitazone, and glyburide study

TABLE 2 Overall Summary of Findings for Selected Adverse Events[a]

Comparison	Hypoglycemia	GI Events	CHF	Fractures
Metformin versus				
TZD	ND ●●	Favors TZD ●●●	ND ●●	Favors MET ●●●
SU	Favors MET ●●●	Favors SU ●●	Favors MET ●●	Unclear ●
DPP-4 inhibitor	ND ●●●	Favors DPP-4 ●●	IE	IE
Meglitinides	Favors MET ●●	Favors MEG ●	IE	IE
GLP-1 agonists	IE	IE	IE	IE
MET + TZD	Favors MET ●●	Favors MET + TZD ●●	IE	Favors MET ●
MET + SU	Favors MET ●●	Favors MET + SU ●●	IE	Unclear ●
MET + DPP-4 inhibitor	ND ●●	Unclear ●	IE	Unclear ●
MET + meglitinides	Favors MET ●	Unclear ●	IE	IE
TZD versus				
Rosi	Favors Rosi ●	IE	Unclear ●	IE
SU	Favors TZD ●●●	ND ●●●	Favors SU ●●	Favors SU ●●●
DPP-4 inhibitor	IE	IE	IE	IE
Meglitinides	Favors TZD	Unclear ●	IE	IE
GLP-1 agonist	IE	IE	IE	IE
SU versus				
DPP-4 inhibitor	Favors DPP-4	IE	IE	IE
Meglitinides	Favors MEG	IE	IE	IE
GLP-1 agonist	Favors GLP-1	Favors SU ●	IE	IE

Symbol legend: ● = low strength of evidence; ●● = moderate strength of evidence; ●●● = high strength of evidence.

[a]Derived from Table 8 (pages 121-122) in Bennett WL, Wilson LM, Bolen S, et al. Oral diabetes medications for adults with type 2 diabetes: an update. Rockville, MD: Agency for Healthcare Research and Quality; March 2011.[1] A total of 7 categories of adverse events were reported including liver injury, macular edema, and pancreatitis and cholecystitis in addition to hypoglycemia, GI events, CHF, and fractures.

CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4 inhibitor; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; IE = insufficient evidence; MEG = meglitinide; MET = metformin; ND = no difference; Rosi = rosiglitazone; SU = sulfonylurea; TZD = thiazolidinedione.

arms for the outcomes of nonfatal myocardial infarction and stroke (with small event rates across treatment groups ranging between 1.0% and 1.7%).[34] However, 2 cohort studies reported that the risk of cardiovascular disease was greater in patients treated with rosiglitazone versus metformin.[68-69] A 6-year retrospective cohort study of newly diagnosed patients with diabetes was based on Taiwan's National Health Insurance records.[68] Compared with metformin, rosiglitazone was associated with higher risks for myocardial infarction (HR = 2.09, 95% CI = 1.36-3.24), angina pectoris (HR = 1.79, 95% CI = 1.39-2.30), and transient ischemic attack (HR = 2.57, 95% CI = 1.33-4.96). Mixed findings were reported in studies that evaluated cardiovascular disease morbidity in patients treated with metformin versus a sulfonylurea.

For microvascular complications of diabetes, namely retinopathy, nephropathy, and neuropathy, most of the evidence was insufficient to formulate meaningful conclusions regarding the findings. No studies included in the AHRQ review evaluated the outcomes of diabetic retinopathy or neuropathy in patients treated with different monotherapies and few studies addressed the outcome of nephropathy. Two large trials with a moderate strength of evidence demonstrated that pioglitazone had favorable effects on renal function compared with metformin.[14,70] Both trials reported a decline in urinary albumin-to-creatinine ratios in patients receiving pioglitazone by 15% and 19%, respectively.[14,70] However, it is unclear whether lower albumin-to-creatinine ratios translated to a reduction in nephropathy rates.

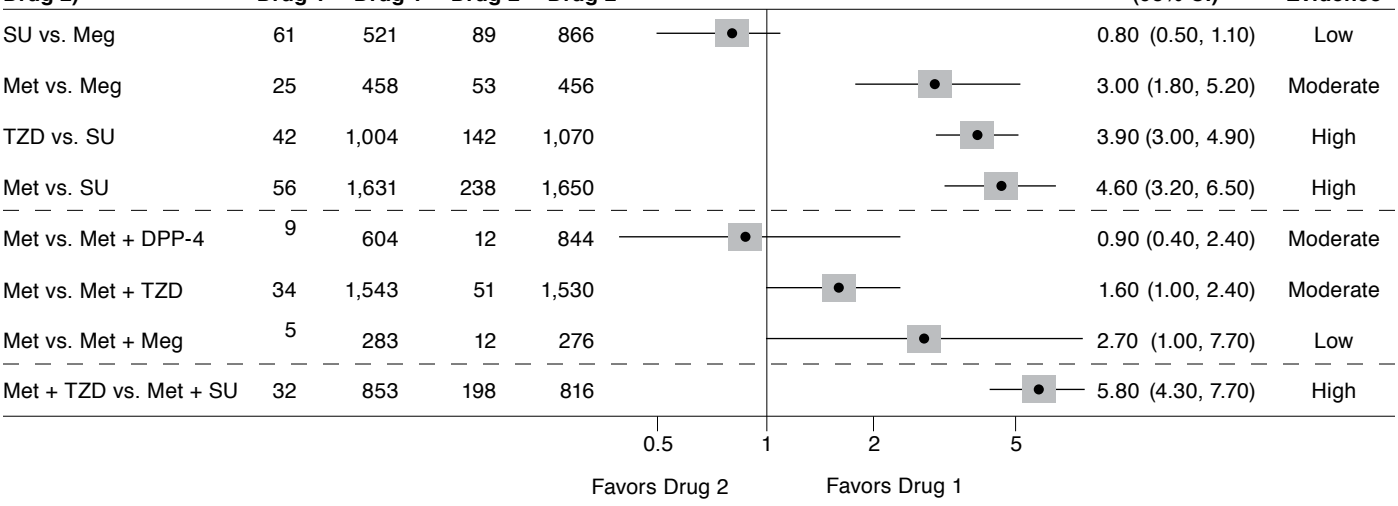
Comparative Safety Risks of Monotherapies

The AHRQ review included studies that evaluated the comparative effects of oral diabetes monotherapies on hypoglycemia and other adverse drug effects, including liver injury, congestive heart failure (CHF), cancer, hip and nonhip fractures, acute pancreatitis, cholecystitis, and GI effects. Conclusions regarding many monotherapy comparisons were precluded due to insufficient evidence. The most commonly reported adverse events were hypoglycemia and GI events (Table 2).

Comparative Effects of Monotherapies on Hypoglycemia. Outcomes for hypoglycemia were based on 88 studies, including 80 RCTs, 7 cohort studies, and 1 nonrandomized trial. Results from multiple trials indicate a 3- to 4-fold increased risk of mild-to-moderate hypoglycemia with sulfonylureas or meglitinides when compared with metformin (Figure 4).[12,21-23,25-27,32,33,36-39,71] In the ADOPT trial, the number of self-reported hypoglycemic events did not differ significantly among patients treated with metformin (11.6%) versus rosiglitazone (9.8%). However, both metformin and rosiglitazone were associated with significantly lower reports of hypoglycemia compared with glyburide (38.7%).[34] Rates of hypoglycemic

FIGURE 4 Pooled Odds of Mild and/or Moderate Hypoglycemia by Monotherapy and Combination Therapy Comparisons[a]

Comparison (Drug 1 vs. Drug 2)	# Events Drug 1	Total N Drug 1	# Events Drug 2	Total N Drug 2	Odds Ratio (95% CI)	Strength of Evidence
SU vs. Meg	61	521	89	866	0.80 (0.50, 1.10)	Low
Met vs. Meg	25	458	53	456	3.00 (1.80, 5.20)	Moderate
TZD vs. SU	42	1,004	142	1,070	3.90 (3.00, 4.90)	High
Met vs. SU	56	1,631	238	1,650	4.60 (3.20, 6.50)	High
Met vs. Met + DPP-4	9	604	12	844	0.90 (0.40, 2.40)	Moderate
Met vs. Met + TZD	34	1,543	51	1,530	1.60 (1.00, 2.40)	Moderate
Met vs. Met + Meg	5	283	12	276	2.70 (1.00, 7.70)	Low
Met + TZD vs. Met + SU	32	853	198	816	5.80 (4.30, 7.70)	High



[a]*Reproduced from Figure 4 (page 608) in Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011;154(9):602-13.*[141] *Error bars represent 95% confidence intervals.*

CI = confidence interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; Meg = meglitinide; Met = metformin; SU = sulfonylurea; TZD = thiazolidinediones.

events were also similar in studies comparing metformin with DPP-4 inhibitors.[41-43]

Overall, sulfonylureas were associated with a 3-7 fold increase in hypoglycemic events compared with metformin, thiazolidinediones, or DPP-4 inhibitors. Pooled results from 5 studies found an increased risk of hypoglycemia among patients receiving sulfonylureas compared with a thiazolidinedione (OR = 3.9, 95% CI = 3.1-4.9).[12,48,49,50,72,73] In 1 large RCT comparing the sulfonylurea glipizide with the DPP-4 inhibitor sitagliptin, 17% of patients receiving glipizide experienced mild-to-moderate hypoglycemia; however, no cases of hypoglycemia were reported for participants in the sitagliptin group.[74] Pooled results from 6 trials comparing sulfonylureas and meglitinides found no significant differences in hypoglycemia among participants.[63,75-79] Sulfonylureas were associated with a significantly higher incidence of hypoglycemia compared with the GLP-1 agonist, liraglutide.[45-47] While there were some differences in the drug classes for mild-to-moderate hypoglycemia, the incidence of severe hypoglycemia did not differ among the various monotherapies.

Comparative Effects of Monotherapies on Other Adverse Events. No significant treatment-group differences were found in the few studies that evaluated liver injury (specific outcomes included liver enzyme abnormalities, incidence of liver failure, or hepatitis). This conclusion applies to comparisons of metformin and thiazolidinediones or sulfonylureas, rosiglitazone and pioglitazone, and thiazolidinediones and sulfonylureas.

Congestive Heart Failure (CHF). Eighteen studies reported on the comparative effects of oral diabetes medications on congestive heart failure (CHF). Moderate strength of evidence showed higher rates of CHF rates among patients treated with a sulfonylurea versus metformin.[80-84] In studies comparing rosiglitazone and pioglitazone, findings were inconsistent and unclear regarding comparative risks of CHF.[68,81,85,86] In a meta-analysis of 4 RCTs, the risk of CHF was higher for patients treated with thiazolidinediones versus sulfonylureas (RR = 1.68, 95% CI = 0.99-2.85) with borderline statistical significance.[34,51,72,87]

Cancer. For the outcome of cancer, the strength of evidence was low and did not allow for definitive conclusions to be made. Three studies reported cancer outcomes in patients treated with different monotherapies. In a single retrospective cohort study of more than 62,000 patients, a higher risk of cancer was reported among patients taking sulfonylureas versus metformin (HR = 1.36, 95% CI = 19 to 1.54, $P < 0.001$).[88] Studies comparing either metformin with meglitinides or sulfonylureas with thiazolidinediones found no significant treatment-group differences in cancer incidences.[49,71]

Fractures. Six studies, including 4 RCTs and 2 observational studies, compared monotherapy regimens and reported the incidence of fractures. In the ADOPT trial, the risk of fracture was greater with rosiglitazone compared with metformin or glyburide over 4 years (HR = 1.57, 95% CI = 1.13-2.17 and HR = 2.13, 95% CI = 1.30-3.51), respectively.[89] Fracture rates among women in the ADOPT trial (n = 1,840) were 9.3% in the rosiglitazone group, 5.1% in the metformin group, and 3.5% in the glyburide group. Other studies found no significant difference in fractures among patients receiving metformin versus thiazolidinediones or sulfonylureas.[18,21,80,89]

Another RCT found no differences in fracture rates among patients taking pioglitazone or glyburide.[49,89] In a prospective study, thiazolidinediones were associated with a slightly greater risk of fractures compared with sulfonylureas.[90] Moreover, compared with men, women taking pioglitazone (HR = 1.70, 95% CI = 1.30-2.23, $P < 0.001$) or rosiglitazone (HR = 1.29, 95% CI = 1.04-1.59, $P = 0.02$) were at a higher risk of fractures.

Pancreatitis. Three 6-month trials found no significant differences in rates of acute pancreatitis for comparisons of the GLP-1 agonist liraglutide with either (a) the sulfonylureas glimepiride or glyburide or (b) the DPP-4 inhibitor sitagliptin.[47,91,92] In these studies, pancreatitis was reported in 0-2 patients. Two RCTs reported results related to the incidence of cholecystitis for type 2 diabetes oral monotherapies. No significant differences were noted among patients taking thiazolidinediones compared with metformin or with sulfonylureas.[16,72] Cases of cholecystitis were extremely rare.

Gastrointestinal (GI) Side Effects. GI adverse effects were more commonly reported among patients receiving metformin compared with any other medication, including sulfonylureas, thiazolidinediones, and DDP-4 inhibitors.[11,14,16,18,21-25,27,28,30,32-34,36-38,41-43,71] In the metformin groups, the most common GI problem was diarrhea, followed by nausea and abdominal pain. No significant differences were noted for the incidence of GI adverse events in comparisons of thiazolidinediones with sulfonylureas or meglitinides.[34,48,49,72] In a single RCT, rates of GI events were similar between patients treated with sulfonylureas or GLP-1 agonists.[46] However, in another RCT, GI events affected approximately 50% of patients receiving the GLP-1 agonist liraglutide compared with 26% of patients receiving sulfonylureas.[47] Nausea, vomiting, and diarrhea were reported in approximately 29%, 10%, and 16% of the liraglutide group, respectively, compared with 8.5%, 3.6% and 8.9% of patients receiving sulfonylureas.[47]

Combination Therapy Comparisons

This section summarizes the AHRQ review findings from studies that compared (a) monotherapy with 2-drug combination therapy and (b) various 2-drug combinations with each other. The specific medication comparisons are listed in Table 1. Major findings for the comparative benefits and risks of combination therapies are presented as follows.

Comparative Effects of Combination Therapies on A1c

Compared with monotherapies, all combination therapies resulted in significantly greater reductions in A1c. Studies comparing metformin alone with metformin in combination with a sulfonylurea, a DPP-4 inhibitor, or a thiazolidinedione[8,11,18,20,21,23-27,30-33,40,43,93-105] showed improved A1c in the 2-drug combinations with pooled mean differences from meta-analyses ranging from 0.66% to 1.00% (Figure 1). Median A1c change from baseline ranged from –0.8% to –1.6% in the metformin combination arms.

Most direct comparisons of metformin combination therapies indicated a similar magnitude of A1c reduction of about 1 absolute percentage point. For example, the between-arm difference was 0.06% in a pooled analysis comparing metformin plus a thiazolidinedione vs metformin plus a sulfonylurea (95% CI = –0.17% to 0.06%) with moderate strength of evidence.[106-111] Although the strength of evidence was low, other studies also reported similar reductions in A1c between groups treated with metformin plus another oral medication. A 26-week RCT compared metformin plus sitagliptin with metformin plus liraglutide in 2 dosing arms (1.2 mg and 1.8 mg).[92] Metformin plus liraglutide arms lowered A1c to a greater extent compared with metformin plus sitagliptin (between-group differences were –0.34% and –0.60% in comparisons with the lower- and higher-dosing arms, respectively).

Comparative Effects of Combination Therapies on Body Weight

Used as monotherapy, metformin was associated with significantly less weight gain than combinations of metformin and a thiazolidinedione (pooled mean difference = –2.2 kg) or a sulfonylurea (pooled mean difference = –2.3 kg, Figure 2).[11,23,24,26,27,30-33,94,95,97,100-102] In contrast, weight change did not differ significantly in a pooled analysis of studies comparing metformin with metformin plus a DPP-4 inhibitor.[35,34,43] The combination of metformin and a GLP-1 agonist was associated with decreased weight in comparisons with metformin plus a sulfonylurea, metformin plus a thiazolidinedione, and metformin plus a DPP-4 inhibitors.[102,112-114] Metformin plus sulfonylurea had a more favorable effect on weight compared with both the combinations of a thiazolidinedione plus sulfonylurea (between-group difference of –3.2 kg, 95% CI = –5.2 kg to –1.1 kg) and metformin plus a thiazolidinedione (between-group difference of –0.9 kg, 95% CI = –1.3 kg to –0.4 kg). Both comparisons had moderate strength of evidence. (Figure 2).[70,106-109,115,116]

Comparative Effects of Combination Therapies on Lipid Outcomes

Compared with metformin alone, the addition of rosiglitazone

to metformin increased LDL-C, with a pooled between-group difference of –14.5 mg per dL in 7 RCTs (Figure 3).[11,95-98,100,117] A meta-analysis of 4 trials indicated that LDL-C was reduced to a greater extent in patients treated with metformin plus a sulfonylurea than with metformin plus rosiglitazone (Figure 3).[103,107,111,118]

Based on a meta-analysis of 7 RCTs[11,95-98,100,117] that evaluated HDL-C, levels increased more in patients treated with metformin plus rosiglitazone than with metformin monotherapy; the pooled mean difference was 2.8 mg per dL (95% CI = 2.2-3.5 mg per dL). No significant differences were observed in a pooled analysis of studies that evaluated HDL-C changes associated with metformin monotherapy versus combinations of metformin and DPP-4 inhibitors.[41,43,95,104] Combinations of metformin with thiazolidinediones increased HDL-C compared with metformin plus a sulfonylurea. In a pooled analysis of 4 RCTs, metformin plus rosiglitazone was associated with a greater mean increase of 2.7 mg per dL (95% CI = 1.4-4.1 mg per dL).[106,107,111,118] In 2 RCTs, HDL-C increased in metformin plus pioglitazone arms and decreased in metformin plus sulfonylurea arms.[109,119] The between-group differences were 5.1 mg per dL ($P < 0.001$) and 5.8 mg per dL ($P < 0.001$), respectively.

In studies that evaluated triglycerides, metformin monotherapy decreased levels more than the combination of metformin plus rosiglitazone.[11,95-98,100,117] The metformin and rosiglitazone combination had similar effects on triglycerides when compared with a combination of metformin and sulfonylurea.[106,107,111,120] In contrast, metformin plus pioglitazone decreased triglyceride levels by about 15 mg per dL compared with metformin plus a sulfonylurea.[109,119]

Comparative Effects of Combination Therapies on Long-Term Clinical Outcomes

Overall, the review identified low or insufficient evidence for most comparisons regarding the outcomes of all-cause mortality, cardiovascular morbidity, and microvascular disease.

The multinational RECORD study was an open-label noninferiority multicenter RCT involving 4,447 participants with type 2 diabetes taking either metformin or a sulfonylurea randomly assigned to metformin plus rosiglitazone, sulfonylurea plus rosiglitazone, or metformin plus sulfonylurea. The primary outcomes were cardiovascular hospitalization or death.[121] For the outcomes of all-cause mortality and cardiovascular mortality, the 2 groups randomized to rosiglitazone were combined and analyzed against the metformin and sulfonylurea combination. A similar number of all-cause and cardiovascular deaths were reported in the rosiglitazone and metformin plus sulfonylurea combination group with a mortality HR of 0.86 (95% CI = 0.68-1.08) and 0.84 (95% CI = 0.59-1.18) for those in the rosiglitazone group, respectively, compared to those in the metformin plus sulfonylurea group.[121]

Among 8 pooled RCTs comparing metformin with a combination of metformin and thiazolidinediones, the odds ratio for ischemic heart disease events was 0.43 (95% CI = 0.11-1.10) for the metformin arm compared with metformin plus thiazolidinedione arm; however, this was not significant.[11,96-98,100,117,122]

Comparative Safety Risks of Combination Therapies

The AHRQ review included studies that evaluated the comparative effects of combination therapies on hypoglycemia and other adverse drug effects, including liver injury, congestive heart failure (CHF), cancer, hip and nonhip fractures, acute pancreatitis, cholecystitis, and GI effects. The majority of the conclusions are based on evidence that is either high or moderate in strength.

Comparative Effects of Combination Therapies on Hypoglycemia

Risks for hypoglycemia were higher for patients treated with combination therapy compared with monotherapy. Pooled results from 8 RCTs indicated an increased risk of hypoglycemia associated with metformin plus thiazolidinediones compared with metformin alone with an OR of 1.6 (95% CI = 1.0-2.4);[11,94-97,99,100,117] the grade of evidence was rated as moderate. High strength of evidence supported an average 6-fold higher risk of hypoglycemia from metformin combined with sulfonylurea (range of relative risk was 1.6 to 20.8); however, substantial heterogeneity between these trials precluded meta-analysis.[21,23,25,26,30,32,33,101,102] Comparisons of metformin alone versus metformin plus a DPP-4 inhibitor yielded mixed results; sitagliptin added to metformin did not increase the risk of hypoglycemia but saxagliptin added to metformin slightly increased the risk.[40,41,43,95,103-105] Moderate grade of evidence showed similar risk of hypoglycemia for DPP-4 inhibitor added to metformin versus metformin alone.

For direct comparisons of various combination therapies, the incidence of hypoglycemia was lower for metformin plus thiazolidinediones compared with other metformin combinations or compared with the thiazolidinediones plus sulfonylureas.[107-109,111,119,123,124]

Two small studies found no significant differences in hypoglycemia for metformin combined with thiazolidinediones compared with metformin combined with GLP-1 agonists or DPP-4 inhibitors, respectively.[113,125] A small study with low-grade evidence found that the addition of insulin glargine to metformin was associated more frequent hypoglycemia (defined as fasting blood glucose < 3.3 mmol per L [59.4 mg per dL]) but not severe hypoglycemia, compared with the addition of the injectable GLP-1 agonist exenatide added to metformin.[126] A study with a high strength of evidence found increased rates of mild-to-moderate hypoglycemia among patients receiving metformin plus sulfonylureas compared with thiazolidinediones plus sulfonylureas (RR = 1.3, 95% CI = 0.9-2.0).[70]

Comparisons of metformin plus sulfonylurea with various other combination therapies for type 2 diabetes were also

analyzed. The definition of severe hypoglycemia differed across studies but was most commonly referred to as hypoglycemia which requires assistance for resolution. A 2-fold increase in the risk of mild-to-moderate hypoglycemia, but not severe hypoglycemia, was found among patients taking a combination of metformin and meglitinides.[127,128] In addition, mild-to-moderate hypoglycemia was also more common among patients receiving metformin plus insulin, liraglutide, or repaglinide compared with patients taking metformin plus sulfonylureas.[102,129,130] Two studies noted a 7-9 fold increased risk of hypoglycemia among patients receiving metformin plus sitagliptin compared with metformin and sulfonylureas.[131,132] Finally, hypoglycemic events were studied for combinations of metformin and various insulins. Moderate grade evidence showed a modestly lower risk of hypoglycemia when metformin was combined with basal insulin or glargine, rather than a premixed insulin such as lispro 75/25 or aspart 70/30 (but not lispro 50/50), which was associated with an increased risk of mild-to-moderate hypoglycemia compared with metformin.[133-138]

Comparative Effects of Combination Therapies on Other Adverse Events

Among several RCTs, no adverse events related to the liver were noted for treatment with various drug combinations including metformin combined with sulfonylureas or thiazolidinediones, or the thiazolidinediones combined with sulfonylureas.[70,109,110] The RECORD study found that patients taking rosiglitazone in combination with either a sulfonylurea or metformin had double the risk of CHF compared with patients receiving a combination of sulfonylurea and metformin.[121] A short-term trial in Germany noted that rates of CHF were higher among patients taking thiazolidinedione and sulfonylurea compared with patients receiving thiazolidinedione and metformin.[124] No differences in CHF were noted between combinations of metformin with either daily doses of long-acting insulin glargine or rapid-acting insulin lispro.[133]

Evidence for the outcome of cancer was graded as low or insufficient for all comparisons because of few to no studies and few events if any. Two trials reported outcomes related to the incidence of cancer among patients taking metformin alone or in combination with sulfonylureas or DPP-4 inhibitors. While no reports of cancer were associated with combination treatment groups, 3 cases were noted in the metformin monotherapy group.[88,103]

High strength of evidence showed that thiazolidinediones in combination with other medications were associated with higher fracture risk compared with metformin alone or in combination with a sulfonylurea. The RECORD trial reported a higher incidence of bone fractures in the 2 combined rosiglitazone arms compared with metformin plus a sulfonylurea (2.3% vs. 1.6%).[121] The comparison of the rosiglitazone combination therapy arms with the combination metformin plus sulfonylurea arms yielded a risk ratio of 1.57 (95% CI = 1.26-1.97, $P < 0.001$). Similar to the ADOPT trial, the relative risk of fractures was higher among women compared with men taking metformin versus rosiglitazone monotherapy (RR = 1.82, 95% CI = 1.37-2.41 vs. RR = 1.23, 95% CI = 0.85-1.77). Unlike hip or femur fractures, upper and lower limb fractures were the predominant type of fracture occurring.[121] No differences in fractures were noted in studies comparing metformin monotherapy with metformin plus pioglitazone, glyburide, or sitagliptin.[18,21,103]

Twenty-five RCTs compared rates of gastrointestinal events between metformin monotherapy with combination therapies with metformin.[11,18,20,21,23-25,27,30,32,33,36,37,41,94-98,102-105,117] Similar rates of GI events were noted among patients taking metformin compared with patients receiving metformin plus thiazolidinediones, or plus the DPP-4 inhibitors.[11,18,41,94-98,103-105,117]

In comparisons of 2-drug combinations, overall, few studies were identified. Four RCTs, which examined GI adverse events between metformin plus a thiazolidinedione and metformin plus a sulfonylurea, showed inconsistent results.[107,109,111,120] One RCT compared metformin and rosiglitazone with metformin and exenatide and found a higher incidence GI events in the exenatide group.[113] However, compared with metformin plus sulfonylureas, the combination of metformin plus GLP-1 agonists (liraglutide, exenatide) had similar rates of GI events.[102,112]

Subpopulation Analyses

Few studies were designed with sufficient power to assess the comparative effectiveness and safety of oral diabetes medications across different patient subgroups; therefore, no firm conclusions could be reached to answer key question 4. One RCT, which compared metformin plus nateglinide with metformin plus glyburide, reported that mean reduction in A1c was greater for patients with higher baseline A1c levels in both treatment arms.[128] In contrast, another study comparing metformin with glibenclamide found no relationship between baseline A1c levels and target glucose control.[138]

No firm conclusions could be drawn regarding the comparative effectiveness of oral diabetes medications for subgroups of patients characterized by age, sex, or race because of the paucity of available evidence. Low strength of evidence showed that A1c reduction or glycemic control was not related to body mass index[40,42,95,128,139] or duration of diabetes[40,42,95,103] for several comparisons. Two observational studies, which analyzed patients who required higher than median doses of diabetes medications, reported that patients taking high-dose sulfonylureas, but not metformin, had a higher risk for CHF[84] and mortality[140] compared with patients taking lower doses. However, conclusions from these studies are unclear because they were from observational studies which were more likely to have residual confounding, related to the patients' need for higher doses. Finally, few studies reported on outcomes in subpopulations with prior comorbid conditions, such as cardiovascular or renal disease.

Limitations and Future Research Directions

The EPC investigators noted several limitations related to study designs and methods which may limit the applicability of the results. The RCTs had strict inclusion criteria, which excluded patients with comorbidities or certain characteristics that could interfere with the trial protocol and limit the data for patients who have pre-existing risk factors for cardiovascular or renal disease. Furthermore, subgroup analysis is also sparse within clinical trials, and analysis of elderly patients, or those with multiple comorbidities, is lacking. Trials investigating the efficacy and safety of treatments for type 2 diabetes are needed, including additional studies of various drug combinations, as well as trials of both monotherapy and combination therapy with meglinitides, DPP-4 inhibitors, or GLP-1 agonists. Studies designed to analyze the addition of basal or premixed insulin compared with metformin or thiazolidinediones are also lacking. Future research studies should also strive to address noninsulin based therapies that include triple combination regimens.

With regard to adverse events, few trials measured macular edema, cancer, allergic reactions, pancreatitis, and fractures associated with medications for type 2 diabetes. In addition, few trials reporting adverse events had study durations beyond a 2-year timeframe. Many patients remained on antidiabetic medications for decades and certain adverse events, such as CHF and fractures, may take more than 2 years to develop.

The investigators provided recommendations for future research so as to improve upon methodological short-comings associated with trials for oral antidiabetic medications. These recommendations include:

- Conducting between-group comparisons from baseline and providing the range of data presented to improve analysis of findings
- Using predefined outcomes and methods for measuring outcomes to enrich long-term adverse events analysis
- Providing detailed information with regard to procedures for randomization and allocation concealment to enhance the interpretations of results
- Incorporating observational studies of treatments for diabetes which include various doses, timings, and duration of use to expand the real-world applicability of results
- Reporting the number of deaths within trials to present a clearer picture of adverse events
- Specifying which "background" diabetes medications were allowed in studies that included patients who took other "nonstudy" diabetes medications, and stratifying results by the combination therapy, which would include the background medication plus the study drug
- Assessing indirect comparisons by conducting a network meta-analysis to provide a more comprehensive view of the efficacy and safety of medication for the treatment of type 2 diabetes.

Conclusions

Overall, the AHRQ review on the comparative effectiveness of oral diabetes medications for treating patients with type 2 diabetes found that monotherapy treatments had similar efficacies for lowering blood glucose. The findings, not surprisingly, also demonstrated that combination therapies could decrease A1c levels more than monotherapies. Unlike most medications, oral metformin and injectable GLP-1 agonists were not associated with weight gain. Sulfonylureas were associated with the greatest risks of mild-to-moderate hypoglycemia, and 2-drug combinations also had greater rates of hypoglycemia compared with monotherapy. Thiazolidinediones have been associated with increased risks for heart failure, cardiovascular events, and hip and nonhip fractures. Metformin was most commonly associated with gastrointestinal upset. Despite the addition of 41 new studies to the 25 studies reviewed in 2007 report regarding macrovascular and microvascular outcomes, the evidence was judged low strength and insufficient except for metformin which was associated with lower all-cause mortality and cardiovascular-disease mortality (compared with sulfonylureas). For CHF, there was a low strength of evidence indicating that the risks were higher with combination therapy which included rosiglitazone compared with a combination of metformin and sulfonylurea. A moderate strength of evidence indicated a higher risk of CHF for thiazolidinedione monotherapy compared with sulfonylurea.

Although the updated 2011 review contained newer medications and more studies elaborating on the comparative benefits and harms of these agents, the evidence is still sparse regarding long-term outcomes and the comparative efficacy of the oral medications. The available evidence supports the use of metformin as first-line therapy in adults with type 2 diabetes.

Commentary: Payer Perspective in Evaluating Diabetic Medications for Glycemic Control in Type 2 Diabetes

Health plans have focused increasingly on microvacular and macrovascular complications of diabetes as spending on treatment of type 2 diabetes has risen dramatically because of the increasing prevalence of type 2 diabetes and the introduction of more expensive new drug therapies. Since 1995, 9 new classes of diabetic drugs have become available, and many patients are now taking combinations of 2 or more therapies including these new drugs, which further increases costs. Although payers may hope that early investment in newer antidiabetic agents can reduce downstream costs, it has been difficult to measure benefit from these drug expenditures because of a lack of studies on cardiovascular morbidity/mortality in the 2007 AHRQ report. Since then, more studies as well as 2 additional drug classes have become available; however, the results remain inconclusive regarding the benefit of higher expenditures for the newer drugs.

For intermediate outcomes, metformin monotherapy continues to have the greatest effect of the oral antidiabetic agents on A1c reduction and works well in combination with other agents. The updated 2011 AHRQ report found that the newer class of dipeptidyl peptidase-4 (DPP-4) inhibitors did not lower A1c as well as metformin monotherapy. Effect on body weight is an important consideration in therapy for type 2 diabetes, and the updated AHRQ report concluded that the antidiabetic drugs except for metformin and acarbose increased body weight. Metformin was associated with small reductions or no change in body weight compared with weight gain with sulfonylureas (mean difference of –2.7 kg favoring metformin), thiazolidinediones (mean difference of –2.6 kg favoring metformin), and with DPP-4 inhibitors (mean difference of –1.4 kg favoring metformin). Therefore, the mean difference in weight change favored metformin by 1.4 kg to 2.7 kg lower body weight compared with the other medications. Compared with sulfonylureas, the GLP-1 agonists were associated with a mean weight loss of –2.5 kg versus –2.7 kg for metformin compared with sulfonylureas. Among the oral agents, only metformin decreased low-density lipoprotein cholesterol (LDL-C), and metformin had a favorable impact on all 3 lipid types. However, the other antidiabetic agents, alone and in combination with metformin, demonstrated mixed effects, and the GLP-1 agonists were not evaluated for lipid outcomes. Lipids remain another clinical variable of interest in monitoring patients with diabetes.

For macrovascular outcomes, the addition of new studies did not strengthen the evidence, as event rates were still low for previously reviewed classes as well as the 2 new classes, GLP-1 agonists and DPP4-inhibitors. The only substantive evidence for microvascular complications included pioglitazone for nephropathy.

With little definitive evidence to distinguish the newer agents regarding short- and long-term efficacy outcomes, the evidence for adverse events and side effects become more relevant in making distinctions for formulary inclusion and reimbursement. Side effects have been more thoroughly studied for the older than newer drug classes, and hypoglycemia was clearly more evident in patients taking sulfonylureas. Another clear association is the relationship between gastrointestinal side effects and use of metformin. In addition, CHF occurred more frequently among patients taking thiazolidinediones than sulfonylureas. Thiazolidinediones, either in combination or alone, were associated with a 1.5 higher risk for bone fractures compared with metformin monotherapy or in combination with sulfonylureas.

In applying these results to reimbursement decisions for diabetes, the updated evidence does not support changes in strategy. The evidence does support metformin as a first-line treatment in newly diagnosed patients with diabetes, balanced with tolerance for gastrointestinal side effects, primarily diarrhea. Sulfonylureas provide a first-line alternative, for those intolerant or unable to take metformin (e.g., renal dysfunction), with consideration of hypoglycemia risk. The thiazolidinedione class is associated with heart failure and bone fracture risks and is therefore a second-tier alternative. Due to significantly greater costs and the lack of evidence regarding long-term outcomes, the DPP-4 inhibitors and GLP-1 agonists on the market are not favorable as first-line therapies. These drugs come into play when there are effectiveness or tolerance issues with first-line agents, and await further evidence on the impact of weight loss and adherence for long-term outcomes.

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